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Binase induces apoptosis of transformed myeloid cells and does not induce T-cell immune response

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Abstract

Microbial RNases along with such animal RNases as onconase and BS-RNase are a promising basis for developing new antitumor drugs. We have shown that the *Bacillus intermedius* RNase (binase) induces selective apoptosis of transformed myeloid cells. It attacks artificially expressing activated c-Kit myeloid progenitor FDC cells and chronic myelogenous leukemia cells K562. Binase did not induce apoptosis in leukocytes of healthy donors and in normal myeloid progenitor cells. The inability of binase to initiate expression of activation markers CD69 and IFN-γ in CD4+ and CD8+ T-lymphocytes testifies that enzyme is devoid of superantigenic properties. Altogether, these results demonstrate that binase possesses therapeutic opportunities for treatment of genotyped human neoplasms expressing activated *kit*.

Keywords: Binase; Antitumor activity; Apoptosis; Selectivity; Transformed myeloid cells; c-*kit*; T-cell response

Ribonucleases (RNases) are involved in control of gene expression, host defence and physiological cell death pathways. In some cases, RNases selectively attack malignant cells, triggering apoptotic response, and therefore are considered as alternative chemotherapeutic drugs [1–3]. Onconase, a frog (*Rana pipiens*) RNase, has reached phase III of clinical trials [4]. Recent data on the cytotoxic effects of microbial RNases, such as the *Bacillus intermedius* RNase (binase) [5], *Streptomyces aureofaciens* RNase Sa3 [6], and 5K cationic mutant of RNase Sa [7,8] suggest that bacterial RNases are a promising basis for developing new antitumor drugs. In order to be effective therapeutics, RNases have to affect selectively certain targets in cancer cells, which distinguish the latter from healthy ones, and they should not cause undesirable immune reactions. Thus, onconase does not exhibit strong immunotoxicity, it cleaves tRNA and selectively inhibits growth of *ras*-expressing tumor cells [9].

Binase is a highly cationic guanyl-specific RNase that catalyzes cleavage of RNA without a need for metal ions and cofactors. The structure of crystalline binase is known at a resolution of 1.65 Å [10]. We have shown that *ras*-expressing fibroblasts are more susceptible to binase than normal cells [5]. In addition to this important target, mutated in at least 25% of patients with oncological diseases [11], an attractive group of target proteins are the kinases [12]. Binase has no effect on proliferation of v-*fms*- or v-*src*-transformed fibroblasts, expressing receptor and non-receptor tyrosine kinases, respectively [5]. Is Kit, which is an another receptor tyrosine kinase, able to cause the selectivity of the binase effect? Overexpression or constitutive activation of Kit by mutations have been associated with various malignancies (gastrointestinal stromal cell tumors, mastocytosis, certain forms of germ cell

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